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Essers, Dirk ; Schäublin, Martina ; Kullak-Ublick, Gerd A ; Weiler, Stefan

DOI: https://doi.org/10.1007/s00228-018-2589-z

# Statin-associated immune-mediated necrotizing myopathy: a retrospective Analysis of Individual Case Safety Reports from VigiBase

Dirk Essers[1,2], Martina Schäublin[1], Gerd A. Kullak-Ublick[2], Stefan Weiler[2,3]

[1] Swissmedic, Swiss Agency for Therapeutic Products, Bern, Switzerland, [2] Department of Clinical Pharmacology and Toxicology and Regional Pharmacovigilance Centre, University Hospital Zurich, University of Zurich, Switzerland, [3] National Poisons Centre, Tox Info Suisse, Associated Institute of the University of Zurich, Switzerland

**Corresponding Author:**

Stefan Weiler, MD, PhD, Department of Clinical Pharmacology and Toxicology, University Hospital Zurich, Raemistrasse 100, CH-8091 Zurich, Switzerland
Tel.: +41 44 255 2067, E-mail: stefan.weiler@usz.ch

**Running title**: IMNM Pharmacovigilance Study

**Acknowledgement**:

We would like to thank the following authorities for their assistance in providing anonymized case narratives of adverse drug reaction reports:

Health Canada - Canada Vigilance Program
The staff of the US Food and Drug Administration
Australian Pharmacovigilance and Special Access Branch, Therapeutic Goods Administration
Italian Medicine Agency – AIFA Post-Marketing Surveillance Department
Czech State Institute for Drug Control
Hungarian National Institute of Pharmacy and Nutrition
German Federal Institute for Drugs and Medical Devices – Pharmacovigilance Department
Norwegian Medicines Agency - Department of safe use
French regional pharmacovigilance network and the Surveillance Division from the ANSM

The source of the information is the WHO database "VigiBase".
The information comes from a variety of sources and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases.
This information does not represent the opinion of the World Health Organization.

*Abstract*

*Purpose*: Statins represent an effective treatment for hyperlipidaemia. Immune-mediated necrotising myopathy (IMNM), a form of statin myopathy, has recently been described, and is characterized by elevated creatine kinase, presence of antibodies against HMG-CoA and no improvement after drug discontinuation, even with immunosuppressive treatment. Information on IMNM is mainly from case reports and small case series. Therefore, all reported cases of IMNM in VigiBase, the WHO global database of individual case safety reports (ICSRs) including the underlying reporting patterns were analysed to characterize more detailed this adverse drug reaction.

*Methods*: ICSRs of IMNM up to October 1st, 2016 were extracted from VigiBase. Corresponding case narratives were requested from responsible national authorities to maximize the available data. The reports were analysed in terms of reporting criteria, co-reported terms, patient demographics, clinical data, administered medication, latency time, seriousness of the reaction and outcome.

*Results*: 101 deduplicated ICSRs of IMNM were reported until October 2016 from 17 countries. Approximately two third of the cases were from the year 2016. Slightly more males than females were affected (52 [57%] males vs. 39 [42%] females). Median reported patient age was 68 years (range 16−87 years). 91 cases (99%) were classified as serious. Median latency time was 26 months (range 1−288 months). Median creatine kinase value was 6,860 U/L (range 576−35,000 U/L). In total, 8 patients (9%) had recovered from IMNM. Atorvastatin was the most frequently reported statin in 80% of cases.

*Conclusions*: The number of IMNM reports has increased in recent years. IMNM associated with statin treatment seems to occur worldwide. Most IMNM cases were reported with atorvastatin. No dose dependency of statin-associated IMNM pathogenesis was identified.

Keywords: HMG-CoA-reductase inhibitors, rosuvastatin, atorvastatin, pravastatin, simvastatin, muscle pain, immunosuppression, CK elevation, creatinine-kinase, HMG-CoA antibody

## Introduction

Clinical evidence in statin therapy is robust, and medical experts and guidelines recommend this drug class as first-line therapy for the primary and secondary prevention of cardiovascular disease in patients with dyslipidaemia [1, 2]. However, statin intake can be associated with adverse drug effects that can lead to discontinuation. Among these effects, musculoskeletal adverse drug reactions (ADRs) are the most common [3], with a wide spectrum related to statin use, ranging from non-severe muscle pain with or without laboratory findings to serious complications such as rhabdomyolysis. Statin myopathy is typically self-limiting, resolving after treatment discontinuation [4].

Approximately 2–3 out of every 100,000 patients treated with statins develop a necrotizing autoimmune myopathy (IMNM) with the presence of autoantibodies against 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (anti-HMG-CoA) [5]. Anti-HMG-CoA autoantibodies are directed against the catalytic domain of HMG-CoA, a protein located in the membrane of the endoplasmic reticulum which is involved in cholesterol biosynthesis and inhibited by statins [6]. On the other hand anti-HMG-CoA autoantibodies can be detected in statin-naïve patients, indicating this autoimmune condition can also occur in the absence of statin exposure [6, 7].

Patients with IMNM experience myalgia with symmetrical and proximal weakness. Laboratory tests may reveal substantially elevated (>2000 U/L in approximately 90% of cases; normal range <171 U/L) creatine kinase (CK) concentrations [5, 8]. Myopathy might be progressive, even after the discontinuation of statin therapy [5], and represents the main clinical feature which leads to suspicion of an autoimmune myopathy. Treatment options of IMNM include immediate administration of high-dose corticosteroids, other immunosuppressive agents and intravenous immunoglobulins [9].

The Swiss Agency of Therapeutic Products notified health professionals of the new risks associated with statin therapy [10].

Given the lack of larger case series, cohort studies and other studies with broader impact regarding this ADR, we analysed all registered cases of IMNM as well as the associated reporting patterns from VigiBase, the World Health Organization (WHO) global database of individual case safety reports (ICSRs) to better characterize this uncommon ADR of statins.

## Methods

ICSRs with a reported ADR term corresponding to MedDRA preferred term "Immune-mediated necrotising myopathy" was selected as the VigiBase search criterion with an entry date up to October 1st 2016. This preferred term includes the lower-level terms "Immune-mediated necrotising myopathy" and "Immune-mediated necrotizing myopathy". All ICSRs contained at least one suspected statin, other cases were excluded from the study.

VigiBase is the largest global collection of ICSRs. More than 110 countries around the world report ADRs to the WHO Uppsala Monitoring Center (UMC) through their national pharmacovigilance centres (NPVCs) [11]. At national level, health-care professionals (HCPs), pharmaceutical companies and, in some countries, consumers report ADRs to the responsible NPVC. VigiBase primarily collects spontaneous, post-marketing reports to enable the earliest possible detection of ADRs and also allows data collection according to WHO Anatomical Therapeutic Chemical classification [12, 13]. The following details were extracted from the UMC database: patient age and gender, completeness information - indicating how detailed an ICSR was filled in and representing data quality [14], reporting country, reporter qualification, ADR seriousness, indication, drug dosage and treatment dates, route of administration, onset of reaction, adverse reaction and patient outcome. The seriousness criteria in VigiBase are "Death"," Life-threatening", "Caused and prolonged hospitalization", "Disabling/Incapacitating" and "Other", which are also part of ICH E2A criteria.

To obtain a maximum of information for each ICSR, all competent authorities were requested to deliver corresponding case narratives which are not available in VigiBase. Subsequently, 74 narratives from 9 countries were received, and included information on patient demographics (age at ADR onset and gender), seriousness of ICSR, laboratory values (e.g. CK, antibodies), administered drugs, dosages, duration of treatment, onset date, outcome and latency time, which was defined as the time between starting of medication and diagnosis. Individual ICSR case narratives were also reviewed to identify duplicate cases. Where no corresponding case narrative was available, duplicates were identified via the following characteristics: patient age and gender, reported ADR terms and reported medication.

Where the month and year (MM.YYYY) of the start, stop or onset date were reported, we considered the recorded month as a full month (30 days). Where only the year (YYYY) was reported, we counted the recorded year as a full year (365 days). In case of discrepancies between the narrative and the initial coded information, we recoded the data according to the

case narrative. Where two or more statins were administered, the dosage of the last reported statin was used for analysis. Pearson's correlation was used for comparing statin doses and CK values, which as well as autoantibody detection data were extracted from the narratives for analysis.

Where unspecific antibodies, besides IMNM pathognomic HMG-CoA antibodies [5], were documented and CK values were within the normal reference range, the respective case was excluded from the study. Reports without antibody and CK value information were included in the study. The frequency of administration of concomitant medications was also analysed, as well as the co-reported ADR terms.

For descriptive analyses, Microsoft Office Excel (2010) and IBM SPSS Statistics (version 23) for Windows were used.

**Results**

Until October 2016 overall a total of 13.799.728 ICSRs were archived in VigiBase, of which 159 international ICSRs with the preferred term for IMNM were extracted (Figure 1). Of these, 32% were reported between 2012 and 2015 while 68% were from 2016. Fifty-eight reports were excluded as duplicates. One case was excluded because it reported nonspecific antibodies that were not pathognomic for IMNM. In eight cases, no statin use was reported. The remaining 92 reports, from 17 countries (Australia, Belgium, Canada, Czech Republic, France, Germany, Greece, Hungary, Italy, Japan, the Netherlands, Norway, Slovenia, Spain, Sweden, Switzerland and the United States), were used for further analysis. Most reports came from the United States (29%).The overall patient characteristics and those of two subgroups, representing cases from Europe and North America, are presented in Table 1. The cases within these subgroups were found to differ in reporter qualification (Figure 2). Although 52% of European cases were reported by physicians, only 7% of North American cases were reported in this way.

The overall median age of patients was 68 years (range 16 – 87 years) (Table 1).

Overall, slightly more males than females were affected by IMNM incidence (52 [57%] males vs 39 [42%] females; for 1 case, gender was unknown). In Europe, slightly more cases were reported for females than for males, 59 vs 41.The majority of reports (91 [99%]) were classified as serious (Figure 1, Table 1).

Median latency time between start of medication and diagnosis for all 92 cases was 26 months (range 1 – 288) (Table 1).

The overall median CK value was elevated, at 6,860 U/L (range 576–35,000 U/L) (Table 1).

HMG-CoA antibody testing was documented in approximately one third of cases. A positive result was obtained in over 70% of these cases (Table 1).

In total, 8 patients (9%) recovered from IMNM (Table 1).

Table 2 displays the type and number of reported statins, the most frequently reported concomitant medications, as well as the top co-reported terms. Atorvastatin was the most frequently coded statin in 80% of the cases, followed by simvastatin (26%), rosuvastatin (19%) and pravastatin (3%). The median daily atorvastatin dose was 40 mg (range 5–80 mg) for a median time of 36 weeks (range 1–232 weeks). The median daily doses for simvastatin and pravastatin were 40 mg, while median rosuvastatin intake was 20 mg. There was no correlation between administered statin dose and CK value (Pearson's correlation coefficient 0.073, $p = 0.722$ for cases with 1 statin; and −0.108, $p = 0.753$ for two or more statins).
The most frequent concomitant medication was ezetimibe (18 patients [20%]), followed by metformin (11 [12%]), acetylsalicylic acid (10 [11%]), levothyroxine (9 [10%]) and amlodipine (8 [9%]).
In two patients (2%), co-administration of amlodipine and simvastatin was documented. Most frequent co-reported terms were polymyositis and blood creatine phosphokinase increased (each 10% of the patients) followed by myopathy (9%), rhabdomyolysis (7%) and asthenia (5%).

## Discussion

Statin-associated IMNM seems to be a global reported phenomenon with reports worldwide. In our analysis this recently characterized autoimmune disease predominantly occurred in Europe and North America, while only a few reports came from Asia and Australia. Since 32% of our cases were reported between 2012 and 2015 and 68% resulted of reports in 2016, it became obvious that the number of reports increased distinctly. This circumstance might not have been attributed to a higher incidence of the underlying disease in such a short period rather than an increased awareness of the diagnosis "statin-associated IMNM". Possibly an increased awareness of the diagnosis IMNM has led to an increased willingness to report these cases.
Nevertheless in this study the number of European and North American reports were the same they differentiated from their reporter qualification. 52% of European cases were reported by physicians, only 7% of North American cases were reported this way. A possible explication

for differences in reporting qualifications might be the existence of "physician assistants" (PAs) in the United States, which reported most of our cases (29%) [15]. The PAs are semi-autonomous clinicians practicing in partnership with physicians, performing also diagnosis and diagnostic testing [15]. PAs are increasingly valuable reporters to pharmacovigilance systems [16]. These reports classified as ICSRs from "other health professionals" in VigiBase could have been co-responsible of the increasing incidence of North American reports.

In the present study, the administration of atorvastatin, simvastatin and pravastatin implicated in the development of IMNM was in line with previous studies [17, 18, 19]. However, almost one in five patients in our cohort were treated with rosuvastatin before being diagnosed with IMNM, which diverges the findings of other studies. Moreover, only 3% of patients with IMNM were treated with pravastatin in our study.

Atorvastatin and simvastatin, which exhibit similar pharmacological properties in terms of lipophilicity and metabolization via CYP3A4 [20], which possibly could predispose to develop IMNM, were the most frequently reported statins. In contrast, rosuvastatin and pravastatin, which are hydrophilic substances are only partly metabolized in the liver via phase II reactions. Both exhibit minor or no metabolism via the CYP pathway [21].

Higher numbers of IMNM cases related to a specific statin might also be dependent of prescription habits.

In parts of Canada, the country which reported 19% of our ICSRs, at least, atorvastatin is the most frequently prescribed statin [22]. Most reports (29%) from VigiBase were derived from the United States, where simvastatin prescriptions were twice as frequent as atorvastatin prescriptions within the period 2003–2012 [23]. Even if atorvastatin prescription has increased in the United States in recent years, the high proportion of statin-associated IMNM reports related to atorvastatin is difficult to explain through prescribing practices alone.

In our analysis, most patients (80%) with IMNM had previously received atorvastatin. This phenomenon was also observed in the study of Grable-Esposito et al. where 21 of 25 patients (84%) with diagnosis of Statin-associated IMNM were exposed to atorvastatin [19]. In the study of Troyanov et al. from 14 patients diagnosed with statin-associated IMNM, 12 (86%) had previously taken atorvastatin [22]. In a recent published case series from New Zealand, all 4 included patients with the same diagnosis were also previously on atorvastatin [24]. Even though there is some evidence for an increased rate of IMNM cases associated with atorvastatin administration, a class effect of statins cannot be excluded also based on our data.

The administered dose range for all statins was within the approved therapeutic dosage range. In our investigation higher doses of statins were not associated with higher CK values. While dose dependency for the self-limited form of statin myopathy has been established [17, 25], such a relationship cannot be confirmed for myopathies with an autoimmune background [26] also based on our data.

Based on our data, the effect of concomitant medications that potentially interact with statins on the risk for IMNM remains unclear. Pharmacokinetically relevant interactions between statin use and the most frequently co-administrated drugs (ezetimibe, metformin, acetylsalicylic acid and levothyroxine) were not identified. However, the co-administration of amlodipine 10 mg/day has been shown to increase the simvastatin plasma–concentration–time curve (AUC) by 77% for the risk of adverse effects in muscle [27]. Whether this interaction is clinically relevant for IMNM remains questionable based on our data.

Most frequent co-reported terms (polymyositis, blood creatine phosphokinase increased, myopathy, rhabdomyolysis and asthenia) are associated with muscular disorders. Terms of other organ systems were coded infrequently, assuming that other conditions only played a negligible role.

Most cases in the present study were classified as serious, some with life-threatening, disabling or fatal outcomes. These findings support the medical relevance of IMNM and impaired quality of life experience by affected patients. Previous studies have shown that IMNM patients were older than 50 years [5, 17, 28], which is in line with the median age of 68 years in our cohort. A recent review described 100 IMNM patients with an average age of 65 years [29]. Males and females were almost equally affected, a finding similar to other studies [27, 30].
The median latency time between starting of medication and diagnosis in our cohort was 26 months, with a broad range. The duration of statin exposure required to develop IMNM has been reported as an average of 2–3 years [18, 31], which is consistent with our data.

The average CK concentration of 6,860 U/L (normal values: up to 170 U/L in women and 190 U/L in men) with a broad range (576–35,000 U/L) is comparable to previous reports [17, 29].
HMG-CoA antibodies are often, but not necessarily, found in patients with statin-associated IMNM. [17]. Nowadays new diagnostic tests have been established to confirm the diagnosis of

anti-HMG-CoA positive IMNM, which are now commercially available [32]. Therefor a biopsy is no more required to confirm the diagnosis of IMNM in case of a positive HMG-CoA antibody result, but remains necessary to establish diagnosis of antibody-negative IMNM [33]. In our patient cohort, HMG-CoA antibody testing was documented for 32 patients, 23 (72%) of whom had a positive test result. This percentage of positive test results has already been observed in another investigation [34].

**Limitations**

This study was based on spontaneously reported ICSR on statin-associated IMNM. Underreporting, missing data and duplicate cases are well-known issues for this type of report. For completion, we requested corresponding case narratives from respective competent authorities in 16 countries to increase the available information for each case. Nevertheless there is still some information missing. We were thus better able to detect duplicate cases and increase the quality of data in our analysis. Considering that approximately one third (36%) of the cases were eliminated as duplicates, this constitutes an important issue in pharmacovigilance databases, especially in very rare adverse drug reactions. We cannot totally exclude the possibility of any other duplicates. Data in VigiBase and also in the case narratives are anonymized. Moreover, they do not contain the exact treatment information for each IMNM patient and we could not detail on diagnostic or therapeutic procedures due to missing information. In cases, where results from biopsy or antibody testing were not documented to assure diagnosis of statin-associated IMNM, other explanations cannot be totally excluded, although an implied causality of spontaneous reports based on the suspicion of the reporter is usually present. On the other hand there could be reports describing symptoms that could be classified as IMNM, but which are not diagnosed and coded accordingly. This would presumably lead to missed cases. Moreover, health systems differentiate on an international level. Therefore, the comparability of reporter qualifications concerning ADR reporting may be limited.

## Conclusion

Where muscle pain persists despite the discontinuation of HMG-CoA reductase inhibitors, physicians should consider an autoimmune cause alongside established self-limiting statin-associated myopathies. The number of IMNM reports has increased in recent years. Statin-associated IMNM does not seem to be a dose-dependent phenomenon. A class effect of statins cannot be excluded. Most IMNM cases were associated with the substance atorvastatin. Further studies are needed to clarify specific factors of this rare adverse drug reaction.

**Conflict of Interest:** The authors declare that they have no conflict of interest. SW is elected Pharmacovigilance Risk Assessment Committee (PRAC) member of the European Medicines Agency. The opinions expressed are those of the writers, and do not reflect the opinion or policy of the European Medicines Agency.

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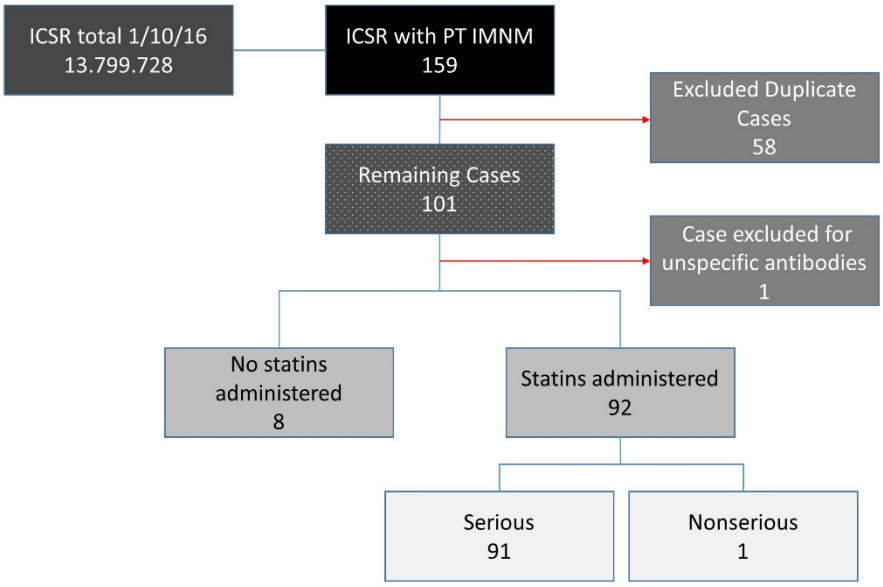


**Figure 1** Flow Chart of VigiBase Analysis

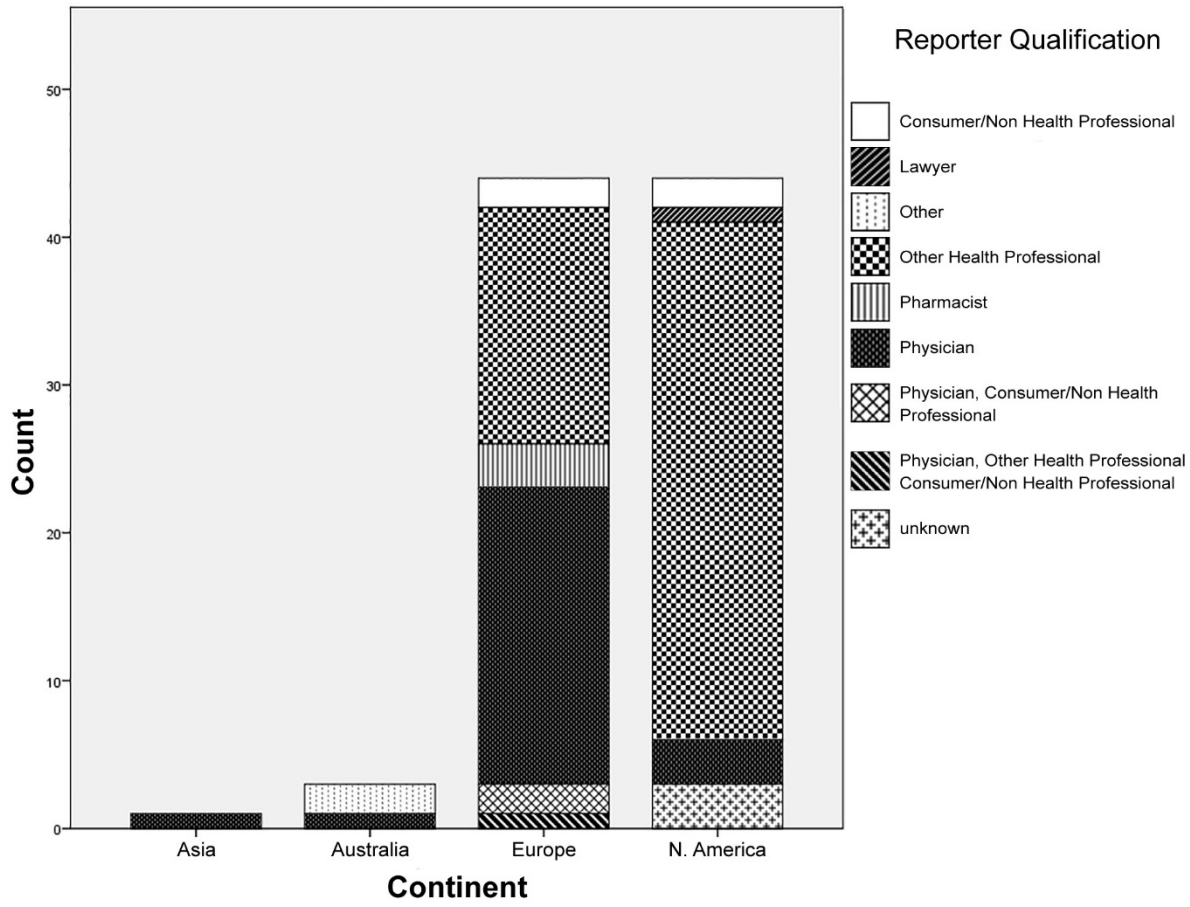


**Figure 2** ICSR Distribution – Reporter Qualification by Continent

| Table 1 Demographic Data – Seriousness - Latency – Test Results- Outcome | | | | | | |
|---|---|---|---|---|---|---|
| | All Cases (n=92) | | European Cases (n=44) | | North American Cases (n=44) | |
| **Characteristics** | **Number** | **%** | **Number** | **%** | **Number** | **%** |
| **Age at onset (years)** | | | | | | |
| Median | 68 | | 68 | | 68 | |
| Range | 16 - 87 | | 55 - 87 | | 33 - 81 | |
| **Sex** | | | | | | |
| Female | 39 | 42 | 26 | 59 | 11 | 25 |
| Male | 52 | 57 | 18 | 41 | 32 | 73 |
| Unknown | 1 | 1 | 0 | 0 | 1 | 2 |
| **Seriousness Criteria** | | | | | | |
| Death | 1 | 1 | 0 | 0 | 1 | 2 |
| Life threatening | 6 | 7 | 5 | 11 | 0 | 0 |
| Caused/prolonged - Hospitalization | 31 | 34 | 23 | 52 | 7 | 16 |
| Disabling/incapacitation | 7 | 8 | 7 | 16 | 0 | 0 |
| Other | 63 | 68 | 23 | 52 | 40 | 91 |
| **Completeness Score** | | | | | | |
| Median | 0.36 | | 0.55 | | 0.32 | |
| Range | 0.1 - 1 | | 0.22 - 1 | | 0.1 - 0.63 | |
| **Latency (months)** | | | | | | |
| Median | 26 | | 25 | | 38 | |
| Range | 1 - 288 | | 1 - 288 | | 1 - 243 | |
| **Creatine Kinase (U/l)** | | | | | | |
| Median | 6860 | | 6000 | | 7913 | |
| Range | 576 - 35000 | | 1344 - 28572 | | 576 - 35000 | |
| **HMG-CoA Antibodies** | | | | | | |
| Test documented | 32 | | 20 | | 11 | |
| Positive | 23 | 72 | 14 | 70 | 9 | 82 |
| **Outcome** | | | | | | |
| Fatal | 1 | 1 | 0 | 0 | 1 | 2 |
| Recovered | 8 | 9 | 7 | 16 | 1 | 2 |
| Not recovered | 9 | 10 | 5 | 11 | 2 | 5 |
| Recovered with sequelae | 6 | 7 | 5 | 11 | 0 | 0 |
| Recovering | 26 | 28 | 15 | 34 | 11 | 25 |
| Unknown | 42 | 46 | 12 | 27 | 29 | 66 |

3 Australian and 1 Japanese case were not included in analyses by continent
Latency: time between starting of medication and diagnosis

| **Table 2 Drugs and co-reported reactions** | | | | | | |
|---|---|---|---|---|---|---|
| | **All cases (n = 92)** | | | | | |
| **Statin coded/patient** | **Number** | **%** | | | | |
| One | 69 | 75 | | | | |
| Two | 20 | 22 | | | | |
| Three or more | 3 | 3 | | | | |
| **Statins administered** | | | **Daily dose (mg)** | | **Duration of intake (months)** | |
| | | | *Median* | *Range* | *Median* | *Range* |
| Atorvastatin | 74 | 80 | 40 | 5.00–80 | 36 | 1–232 |
| Simvastatin | 24 | 26 | 40 | 10.00–80 | 31 | 1–168 |
| Rosuvastatin | 17 | 19 | 20 | 1.25–40 | 13 | 1–114 |
| Pravastatin | 3 | 3 | 40 | 40.00–40 | n.a. | n.a. |
| **Top 5 concomitant medication** | | | | | | |
| Ezetemib | 18 | 20 | | | | |
| Metformin | 11 | 12 | | | | |
| Acetylsalicylic acid | 10 | 11 | | | | |
| Levothyroxine | 9 | 10 | | | | |
| Amlodipine | 8 | 9 | | | | |
| **Top 5 Co-reported terms** | | | | | | |
| Polymyositis | 9 | 10 | | | | |
| Blood creatine phosphokinase increased | 9 | 10 | | | | |
| Myopathy | 8 | 9 | | | | |
| Rhabdomyolysis | 6 | 7 | | | | |
| Asthenia | 5 | 5 | | | | |

n.a. = not available